By virtue of this Amendment, claims 1, 19 (duplicative of claim 18) and 20 are canceled. Due to the cancellation of claim 1, claims 7-10 and 12-14 are amended to be dependent on claim 5 only. Claims 21-25 are added. Support for the new claims can be found throughout the specification as originally filed. Specifically, support for claim 21 can be found at page 8 lines 16-26, page 9 lines 1-5, Examples 2-4 and Figures 3-5. The specification at the cited locations describes that lactoferrin inhibits dermal inflammatory response that is characterized by accumulation of dendritic cells in lymph nodes, by reducing the accumulation of dendritic cells in the lymph nodes. The recitation of "allergen" in claim 22 is also supported by the indicated disclosure. The inclusion of an inflammatory response mediated by "TNF-α" or characterized by "Langerhans cell migration" in claims 23 and 24, respectively, is supported by the entire specification, and more specifically by description of Example 3. The inflammatory disorders recited in claim 25 are supported by the language of claim 13 as originally filed.

An issue of new matter is not raised, and entry of the claim amendments is respectfully requested. The new set of claims relates to the same invention as originally presented. Upon entry of this Amendment, claims 5-10, 12-14, 21-25 are now pending.

Applicants hereby respectfully request reconsideration of the application and allowance of the claims in view of the preceding amendments and the remarks made herein.

Informalities:

Election/Restriction

Claims 2-4 are alleged to be directed to an independent and distinct invention. Applicants hereby cancel claims 2-4 without prejudice and disclaimer. Applicants reserve the right to pursue the cancelled claims in a divisional application.

Claims 11, 15-19 were previously withdrawn from consideration. However, upon the allowance of the generic claim 5, Applicants hereby request rejoinder of claims 11 and 15-19.

Rejection under 35 U.S.C.§ 103

Claims 1, 5-10, 12-14 and 20 have been rejected under 35 U.S.C. §103 as being allegedly obvious over Teng *et al.* in view of various combinations of Nuijens *et al.*, Enk *et al.*, *Penco et al.*, and a Japanese patent application abstract AN 95-340208. The Office argues that the combined teachings of the cited references describe or suggest the methods as instantly claimed. Applicants do not acquiesce to the Office's interpretation of the cited articles or decisions, and do not agree with the grounds of rejection (see detailed discussion below). However, for ease of prosecution, claims 1 and 20 are cancelled. The rejections directed to these two claims are therefore rendered moot.

I. Summary of the Invention:

The claimed invention as defined in Claim 5 encompasses a method of treating an allergen-induced inflammatory disorder by administering to a mammal a therapeutically effective amount of lactoferrin product. Unlike the prior use of lactoferrin to inhibit antimicrobial infections via a well-characterized endotoxin, lipopolysaccharides (LPS), the present invention is based in part on the surprising discovery that lactoferrin inhibits allergen-induced inflammatory response which is independent of LPS. In sum, the claimed invention is directed to a novel use of lactoferrin that is neither described nor suggested by the cited references.

II. Improper Application of Case Law

The Office's analysis as set forth in the Action of December 4, 2000 is flawed in several respects. At the outset, the Office applies an incorrect legal standard for obviousness rejection and misses the essence of the invention.

In the Action, the Office cites *In re Swinehart*, 169 USPQ 226 in support for a rejection under U.S.C. §103. The Office quotes the court's opinion:

> "it is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Id. 229.

Applicants submit that the Office's reliance on the court's decision is misplaced. First, there is no discussion in *Swinehart* with respect to obviousness rejection. The only issue in the case is whether the use of functional language in claims renders the claims indefinite under 35 U.S.C. §112 2nd paragraph. The court reversed the decision of U.S. Patent Office Board of Appeals, and held that functional language alone does not mandate denial of the claims based on indefiniteness. The opinion cited by the Examiner is thus taken out of context, and not applicable for the instant application.

Furthermore, the opinion itself concerns composition claims ("claims drawn to those things") and not method claims (e.g. the use of a particular composition). The *Swinehart* court states a fundamental aspect of patent law: old composition is not patentable by mere recitation of a newly discovered property that is inherent in the old composition. However, an equally fundamental principle, which is ignored by the Office, is that novel and non-obvious use of an existing composition is patentable. Here, the claims at issue are not directed to the composition of lactoferrin *per se*. Rather, the claims are drawn to a method of treating allergen-induced inflammation by administering a therapeutically effective dose of lactoferrin. The ability of lactoferrin to inhibit allergen-induced inflammation, which is distinct from previously characterized anti-antimicrobial activity, is neither described nor suggested by the cited art. The novel use of lactoferrin based on this newly discovered property is nonobvious.

III. Prima Facie Obviousness Has Not Been Established

Turning now to the factual issues of the Action, Applicants submit that the Office has not established a *prima facie* case of obviousness.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness. See, e.g., *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). It is well established that the prior art may not be modified or combined to reject claims as *prima facie* obvious unless there is some motivation in the art to combine and modify the references in the manner described, as well as a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed.Cir. 1986). It is also an established principle that the cited art must effectively suggest all of the limitations of the claimed invention. *In re* Royka, 490 F.2d 1382, 165 USPQ 494, 496 (CCPA 1970).

(a.) The art does not describe or suggest all elements of the claims.

The Primary Reference by Teng et al.:

Teng *et al.* discloses the isolation and characterization of a human lactoferrin cDNA and its encoded protein product (see abstract of Teng *et al.*). To the extent that Teng *et al.* generally describes a method for treating a condition (including skin infection) due to deficiency in lactoferrin, the Office argues that Teng *et al.* teaches "*a method of treating dermal inflammatory disorder*" as instantly claimed (see paragraph 4 at page 2 of the Action). Applicants respectfully traverse.

First, the disease conditions that Teng *et al.* is concerned are not allergen inflicted. Teng *et al.* lists various disorders and specifically characterizes them as deficiencies in lactoferrin (Emphasis added). Thus, Teng *et al.* focuses on eliminating lactoferrin deficiency and restoring the normal lactoferrin level in a subject. However, patients with normal levels of lactoferrin can

still suffer from an allergen-induced disorder. As illustrated in the instant application, inhibition of allergen-inflicted inflammatory response requires administering a therapeutically effective dose of lactoferrin, which exceeds the normal level of lactoferrin *in vivo* (see the Example section of the specification). Emphasizing an entirely different category of disease conditions, it is not surprising that Teng *et al.* does not suggest or even pertain to the use of lactoferrin for treating allergen-induced conditions. As such, Teng *et al.* fails to teach and suggest a necessary aspect of the claimed subject matter.

Second, Teng *et al.* does not describe or suggest treatment of any kind for inflammatory conditions. Although Teng *et al.* lists "skin infection" as a lactoferrin-deficient condition, it does not follow that such infection results in inflammation; nor does it imply that such condition is allergen induced. With respect to the Office's generalization that Teng *et al.* expressly teaches a treatment to *dermal inflammatory disorder* as instantly claimed, Applicants submit that there is a spectrum of skin infections: some do not involve inflammation, and many are not related to allergen at all. To draw any inference from Teng *et al.* that "skin infection" is both caused by an allergen and results in inflammation, is highly speculative and finds no basis in the cited disclosure. The Office's assertion appears to be reached only by "genericizing" both the cited art and the claimed invention until they are forced to overlap.

Noteworthy is also the fact that Teng *et al.* is a non-enabling reference and hence does not qualify as prior art under section 103. The cited text does not teach how to determine or ascertain lactoferrin deficiency in a subject, how to replenish lactoferrin *in vivo*, and how to determine the *in vivo* efficacy of lactoferrin in treating the listed deficiencies. Absent these teachings, one skilled in the art is left with unlimited experimentation in attempt to devise a therapeutic scheme to correct lactoferrin deficiency as Teng *et al.* have hoped to achieve.

Applicants further note that Teng *et al.* fails to teach all aspects of the instant invention as defined in dependent claims 6-10 and 12-14. Specifically, Teng *et al.* does not describe or

suggest that lactoferrin can be used to inhibit inflammatory activity associated with IL-1β or TNF-α. Such deficiency is not cured by the cited secondary references as detailed below.

The Secondary References:

The secondary references, Nuijens *et al.*, AN 95-340208, Enk *et al.*, and *Penco et al.* also do not compensate for or overcome the deficiencies in the teachings of the primary reference by Teng *et al.*

Nuijens *et al.* reports that lactoferrin suppresses IL-1 and TNF-α release from monocytes in response to LPS. See last paragraph at page 287 that is cited by the Examiner. No where in Nuijens teaches or suggests that lactoferrin suppresses IL-1 or TNF-α production in response to an allergen, which mediates through an LPS independent pathway. Therefore, Nuijens *et al.* is not on point and adds nothing to a determination of *prima facie* case of obviousness. Similarly, AN 95-340208 teaches the preparation and use of a lactoferrin composition that confers antimicrobial activity, which again relates to LPS pathway as stated and distinguished in the specification. Consistent with the utility that has previously been described, AN 95-340208 merely states that "*The drug shows antimicrobial effects and causes no side effects.*" As such, AN 95-340208 fails to appreciate the anti-allergen activity of lactoferrin. Indeed, focussing on an entirely different utility, it is not surprising that AN 95-340208 does not teach the novel use of lactoferrin involving its capability to inhibit allergen-induced inflammation, which is the claimed subject matter.

Enk *et al.* observed an augmentation of IL-1β mRNA and TNF-α mRNA levels in Langerhans cells when induced with an allergen. Enk *et al.* concludes that "*These studies demonstrate that Langerhans cell-derived and certain keratinocyte-derived cytokine mRNAs are selectively upreguatlated by allergens in the very early afferent phase of contact sensitivity.*" See last sentence of the abstract. Enk's statement should not be interpreted as establishing a

causal relationship between the elevation of IL-1β or TNF-α mRNA level and the allergen-induced inflammatory reaction. The Office's hasty conclusion that Enk *et al.* teaches "*both IL-1β and TNF-α are responsible for promoting inflammatory activity, including allergen-induced inflammatory activity*" is without factual basis. Applicants respectfully submit that such causal relationship as asserted by the Office is a gross generalization, which departs from the objective teachings of Enk *et al.* Indeed, a close examination of Enk *et al.* reveals a lack of suggestion for a causal role of either IL-1β or TNF-α in allergen-induced contact sensitivity. While Enk *et al.* speculates that cytokines such as keratinocyte derived MIP-2 and IP-10 may be responsible for the *in vivo* activation of Langerhans cell, Enk *et al.* does not list either IL-1β or TNF-α as being responsible for the inflammatory reaction. See the conclusion paragraph of the Introduction section at page 1398[1].

Penco *et al.* is cited for teaching that lactoferrin inhibits IL-1β activity. To the extent that Penco *et al.* discloses lactoferrin inhibits expression of another cytokine, GM-CSF, in IL-1β transfected cells, the Office hastily concludes that lactoferrin inhibits IL-1β. Applicants submit that such assertion lacks factual support and reflects improper hindsight reasoning.

Penco *et al.* tested lactoferrin action on GM-CSF gene expression in two cellular systems: a continuous cell line that constitutively produces GM-CSF and IL-1β, and embryonic fibroblast induced by IL-1β to produce GM-CSF. The researchers found that lactoferrin inhibited GM-CSF mRNA expression in the latter cells and not in the former cell type. The researchers then speculated that "*... lactoferrin plays a negative role in GM-CSF expression at the transcriptional level, perhaps through the mediation of IL-1β.*" Applicants submit that the final

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[1] Enk *et al.* states in the cited location: "In *this study, we demonstrated, in contrast to irritants and tolerogens, contact allergens cause a distinct patter of cytokine production in the early induction phase of contact sensitivity. Some of these factors, including keratinocyte derived MIP-2 and IP-10, may be responsible for the in vivo activation of LCs (Langerhans cell) and for initiating the afferent phase of contact sensitivity.*"

readout of Penco's experiment is alteration of GM-CSF expression, and not change in either IL-1β activity or expression. There is no showing in Penco *et al.* that lactoferrin directly downregulates IL-1β expression. The fact that lactoferrin fails to inhibit GM-CSF expression in cells constitutively expressing IL-1β further casts doubt on the causal relationship between lactoferrin and downregulation of IL-1β. Thus, a fair inference one of ordinary skill in the art could draw is that lactoferrin inhibits IL-1β induced GM-CSF expression.

Also noteworthy is that nothing in Penco *et al.* suggests the relevance, if any, of its *in vitro* test to an *in vivo* application of lactoferrin. Penco's *in vitro* system employs fibroblasts and bladder carcinoma cells (see the Method section). There is not a slightest hint as to whether such a system is indicative of *in vivo* conditions involving allergen stimulation as instantly claimed; nor is there any suggestion that would have prompted one skilled in the art to draw such an implication.

(b). Lack of Suggestion in the Primary and Secondary References to Derive the Claimed Methods

In support for the rejection of claims 5-10, and 12-14 under 35 U.S.C. § 103, the Office contends that the combined teachings of Teng *et al.*, Nuijens *et al.*, Penco *et al.* and AN 95-340208 would render the claimed method of treating allergen-induced inflammatory disorders obvious. Applicants respectfully point out that the Office's analysis is incorrect. A close examination of the cited references reveals that none of the cited references alone or in combination provides any motivation to combine the teachings to derive the claimed invention. Although there are pieces of information relating to lactoferrin deficiency syndromes (Teng *et al.*), the antimicrobial activity of lactoferrin (Nuijens *et al.*, AN 95-340208) and inhibitory action on GM-CSF expression (Penco *et al.*), there is absolutely no teaching on a lactoferrin based treatment for allergen-induced inflammation *in vivo*. Therefore, the references when combined

effectively fail to suggest all of the claimed elements. To hold otherwise will be a hindsight reconstruction of the claimed invention in view of Applicants' own disclosure. Taken together, the Office has not established a *prima facie* case of obviousness.

In view of the foregoing, Applicants believe that the Examiner will now fully appreciate the differences between the present invention and the cited prior art. Because the independent claim 5 is nonobvious over the cited art, so are the dependent claims 6-10 and 12-14 that recite additional limitations.

Finally, Applicants submit that new methods claims 21-25 reciting limitations in addition to the above listed features are also patentable over the cited references. Claim 21 and its dependents require that the dermal inflammatory response is characterized by accumulation of dendritic cells in lymph nodes, and that the administration of lactoferrin product reduces the accumulation of dendritic cells in the lymph nodes. None of the cited references mentions or ever pertains to inhibition of dendritic cell accumulation at an inflammatory site. These new claims 21-25 are also patentable in view of the cited art.

III. CONCLUSION

In view of the amendments and remarks Applicants assert that the specification and claims comport with all of the requirements of 35 USC §103, and Applicants request an early notice of allowance. However, if the Office believes there are any outstanding matters to be resolved, she is invited to telephone the undersigned at the telephone number listed below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 08-3038** referencing docket no. **00138.0041**.

However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: February 27, 2001

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